REMARKS

Claims 1,16, and 31 are amended herein such that they are directed to treatment of hypoxemia in acute lung injury resulting from indirect causes. The amendment is supported by the specification on page 32, lines 25 to 28, which reads "therapeutic agents comprising the anti-IL-8 antibody of the present invention as an active ingredient are useful for hypoxemia in acute lung injury resulting from indirect causes." Thus, the claim amendments are completely supported by the specification and do not introduce new matter.

The Office maintained the rejections under 35 U.S.C § 102(a) and 35 U.S.C § 103(a) over the Folkesson document. In particular, the Office asserts that Folkesson directly teaches or suggests treatment of acute lung injury resulting from indirect causes on page 107, second column, last full paragraph, which allegedly shows that the anti-IL-8 antibody used in the studies was effective for decreasing endotoxin-induced neutrophil influx into the lungs of rabbits. It is respectfully submitted that the rejection is rendered moot by the amendments to claims 1, 16, and 31 as Folkesson fails to disclose or suggest treatment of hypoxemia in acute lung injury resulting from indirect causes which occur systemically.

The claims have been amended so that they are limited to treatment of hypoxemia in acute lung injury, which is a reduction in arterial oxygen pressure (PaO_2) in the lung. As can be seen in Figure 2 and in the description on page 37, lines 6 to 21 of the present application, arterial oxygen pressure was decreased when rabbits suffering from acute lung injury resulting from indirect causes were administered the anti-IL-8 antibody. Thus, administration of the anti-IL-8 antibody reduced the effects of hypoxemia in acute lung injury resulting from indirect causes.

With regard to the Office's statement regarding endotoxin-induced neutrophil influx, Folkesson states "the anti-rabbit-IL-8 antibody used in this study (ARII 8.2) was developed by us to be species-specific and was shown to be affective in decreasing endotoxin-induced neutrophil influx into the plural space of rabbits by >75% (29)." Reference 29 in the Folkesson document is a journal article entitled "Neutralization of IL-8 Inhibits Neutrophil Influx in a Rabbit Model of Endotoxin-Induced Pleurisy," by Broaddus *et al.*, *J. Immunol. 152*: 2960-2967 (1994), which is

submitted with the accompanying Information Disclosure Statement. As can be seen from the title and abstract of Broaddus, this document describes a "pleurisy model," which is a model for observing inflammation outside of the lung. As can be seen from the description bridging page 2963 (right column) to page 2964 (left column) of Broaddus, arterial oxygen pressure (PO_2) did not decrease. Thus, Broaddus does not demonstrate that endotoxin-induced neutrophil influx occurs in conjunction with acute lung injury. Furthermore, Broaddus does not establish that endotoxin-induced neutrophil influx is associated with hypoxemia in the lung, as arterial oxygen pressure did not decrease. Therefore, Broaddus and Folkesson do not show that an anti-IL-8 antibody can decrease endotoxin-induced neutrophil influx for treatment of hypoxemia in acute lung injury resulting from indirect causes.

Furthermore, as noted in the amendment filed 13 September 2001, acute lung injury resulting from acid inhalation is distinct from acute lung injury resulting from indirect causes which occur systemically. First, the specification notes that while aspiration, diffuse pulmonary infection, near-drowning, inhalation of irritant gas, and lung contusion are causes of direct injury, indirect injury results from an entirely different set of causes, such as sepsis syndrome, severe nonthoracic trauma, hypertransfusion during emergency resuscitation, and artificial cardiopulmonary bypass surgery (page 3, line 17 to 22). Second, physicians classify acute respiratory distress syndrome resulting from direct causes as a different condition than acute respiratory distress syndrome resulting from indirect causes, as evidenced in Bernard *et al.*, *Am. J. Respir. Crit. Care Med. Fall 149*: 818-824 (1994), which was forwarded to the Office on 29 September 2000.

Moreover, it is appreciated in the art that while one drug may have an affect on lung injuries resulting from direct causes, that drug may exert a completely different effect on lung injuries resulting from indirect causes. In particular, it has been demonstrated that lidocaine can mitigate the affects of direct lung injury caused by acid aspiration, while on the other hand, the same drug has little effect on indirect lung injury caused by endotoxin infusion. This distinction between direct injury and indirect injury was reported in Nishina *et al.*, *Anesthesiology 88*: 1300-1309 (1998) and Nishina *et al.*, *Anesthesiology 83*: 169-177 (1995), which were forwarded to the

Office on 27 September 2000. Hence, direct injury and indirect injury are classified as two distinct conditions in the art and are clinically divergent.

Thus, Folkesson fails to disclose a method for treating acute lung injury resulting from indirect causes which occur systemically. Furthermore, if the Office argues that Folkesson inherently disclosed the claimed subject matter because there was a possibility that the methods for treating direct lung injury could be used to treat indirect lung injury, it is well-settled legal precedent that inherency does not cover probabilities or possibilities. *Continental Can Co. U.S.A., Inc. v. Monsanto Co.*, 948 F2d 1264, 1268-69, 20 USPQ.2d 1746, 1749 (Fed. Cir. 1991) citing *In re Oelrich*, 666 F2d 578, 581, 212 USPQ 323, 326 (CCPA 1981). Thus, Folkesson does not directly or inherently disclose treatment of acute lung injury resulting from indirect causes.

Further, the pending claims are not obvious in view of Folkesson because the document never teaches or suggests treatment of acute lung injury resulting from indirect causes. Specifically, endotoxin-induced neutrophil influx observed in the pleurisy study of Broaddus is inapplicable to treatment of hypoxemia in acute lung injury because arterial oxygen pressure never decreased and measurements were observed outside of the lung. Also, the studies reported by Nishina *et al.*, which are described above, show that there would have been no expectation for successfully treating hypoxemia in indirectly caused acute lung injury based on the teachings of Folkesson because the art taught that treatments for directly caused acute lung injury were not effective for treating indirectly caused acute lung injury. Thus, the claimed subject matter is inventive over Folkesson.

Conclusions

Claims 1, 16, and 31 are amended such that they are directed to treatment of hypoxemia in acute lung injury resulting from indirect causes which occur systemically. Folkesson never teaches treatment of hypoxemia in acute lung injury because the referenced studies in Broaddus were incapable of detecting hypoxemia - they observed no change in arterial oxygen pressure outside of the lung and never detected a change in arterial oxygen pressure inside of the lung. Thus, Folkesson never discloses treatment of hypoxemia in acute lung injury resulting from indirect causes. Also, Folkesson fails to render the claimed subject matter obvious because (1) it

never suggested treating indirectly caused lung injury with an anti-IL-8 antibody and (2) it was known in the art that treatments of directly caused acute lung injury were not effective for treating indirectly caused acute lung injury. For these reasons, it is respectfully requested that the rejections of the claims under 35 U.S.C. § 102(a) and 103(a) be withdrawn.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing Docket No. 350292000500. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

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EXHIBIT A

Please amend claims 1, 16, and 31 as follows:

1. (Amended) A therapeutic agent for treatment of hypoxemia in acute lung injury resulting from indirect causes which occur systemically and thereby injure the lung indirectly comprising anti-IL-8 antibody as an active ingredient in an amount effective to treat the acute lung injury.

16. (Amended) A process for the production of a therapeutic agent for treatment of hypoxemia in acute lung injury resulting from indirect causes which occur systemically and thereby injure the lung indirectly comprising mixing anti-IL-8 antibody in an amount effective to treat the acute lung injury with an pharmaceutical acceptable carrier.

31. (Amended) A therapeutic method for treatment of hypoxemia in acute lung injury resulting from indirect causes which occur systemically and thereby injure the lung indirectly, which method comprises administering anti-IL-8 antibody to a subject in need of said therapy.